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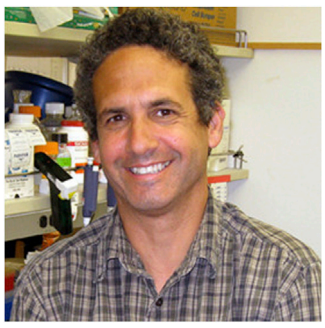
Stem Cell Energetics

Metabolism Defines Stem Cells

Emmanuelle Passegué
University of California, San Francisco

One of the most fascinating observations in the last few years in the field of hematopoietic stem cell (HSC) biology is that quiescence, the physiological state of dormancy that maintains the self-renewal of adult blood-forming HSCs, is governed primarily by metabolism. Hence, self-renewing HSCs rely mainly on anaerobic glycolysis for energy production, with a dash of fatty acid metabolism to support complex fate decisions like symmetric versus asymmetric divisions. At the same time, oxidative phosphorylation by the mitochondria has to be actively prevented to maintain cell quiescence. In contrast, HSC differentiation and active blood production requires the engagement of the TCA cycle to generate high levels of ATP, as well as increased production of reactive oxygen species (ROS) as a byproduct of mitochondrial activity, to help jump-start lineage commitment programs. While the hunt for the ultimate combination of surface markers that solely enrich for engrafting HSCs is still on, I have come to redefine HSCs based on their metabolic plasticity and ability to transition from dormancy to activity over a continuum of marker expression. Hence, in my view, the metabolic state and quiescent status, rather than the phenotypic identity, are the most important criteria for defining engrafting HSCs. This updated operational definition opens new perspectives for understanding HSC function in normal and disease contexts and for expanding engrafting HSCs in vitro for clinical applications.

Dynamic PSC Mitochondria

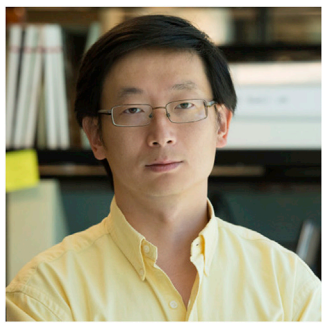


Michael Teitell
University of California, Los Angeles

Cells consume nutrients for sustenance, replication, and function. Pluripotent stem cell (PSC) apportioning of resources for energy and biomolecules regulates self-renewal and differentiation potential. The mitochondrion is central in this metabolic network of life. In naive PSCs, mitochondria are nonfused and perinuclear and generate ATP. Metabolism shifts in primed PSCs to emphasize glycolysis, with ATP hydrolysis maintaining the mitochondrial membrane potential. Upon differentiation, mitochondria fuse into a cytoplasmic network and return to ATP production. With somatic cell reprogramming to pluripotency these processes are reversed.

Many questions about mechanisms and integration of these mitochondrial changes remain unanswered, which could impact cell therapies. For example, what factors control position, network status, turnover, and relationship to the endoplasmic reticulum? When do these changes occur, and how do they impact energetics, Ca^{2+} regulation, Fe/S clusters, and apoptotic sensitivity? How do TCA cycle metabolite levels or differences in growth media affect epigenetic enzymes that regulate gene expression? What sensors establish lineage-specific mtDNA and mass levels? How is respiratory capacity increased with differentiation and lowered with reprogramming? When is mitophagy activated? How are mitochondria integrated with HIFs, which promote self-renewal or differentiation depending upon stimuli? In sum, much remains to be learned about how mitochondria regulate PSC fate.

Endogenous Small Molecules



Sheng Ding
Gladstone Institute

In recent years, it's become clear that "endogenous" small molecules derived from cell metabolism (e.g., metabolites of cellular nutrients and building blocks) contribute to modulation of cell fate (e.g., stem cell differentiation or cancer cell growth) and state. They can function as ligands of receptors, modulators of enzyme activities (e.g., histone modifying enzymes and metabolic enzymes), or participants in protein modifications to directly control cellular signaling and transcriptional, epigenetic, and metabolic mechanisms. Conversely, the generation of different pools of these small molecules at various levels is controlled by cell-type- and state-specific expression of metabolic enzymes, microenvironments (e.g., nutrient input and stress), and certain cellular processes (e.g., autophagy). This interplay constitutes the robustness of cell fate and orchestrates cell fate transition. Consequently, manipulation of cellular metabolism by exogenous small molecules that change a cohort of metabolites provides a powerful approach to controlling cell fate.

Continued efforts in metabolomics and especially in deorphanization of receptors will undoubtedly contribute to increased understanding of the abovementioned mechanisms. This would require comprehensive cataloging of all metabolites, true metabolic profiling of different cell types/states, integration with other molecular "-omics" and cellular functional data sets, and new technology developments in addressing these challenges.

Stem Cell Activation Energetics

Tom Rando
Stanford University

Many somatic stem cells persist in a quiescent state until extrinsic signals induce them to activate, proliferate, and produce differentiated progeny. Typically, while quiescent stem cells are tiny, with scant cytoplasm and few mitochondria, they enact quiescence-specific transcriptional and epigenetic programs. Yet little is known about the bioenergetic requirements of the quiescent state or the metabolic pathways that generate ATP to support those needs. Deciphering this issue will require sensitive and specific probes that distinguish among metabolic pathways and can be used in vivo to address these issues adequately.

By contrast, the activation of stem cells out of quiescence poses an enormous energetic challenge. Support is needed for massive cell growth prior to division and for extensive macromolecular and organelle biosynthesis. Energetic and biosynthetic demands are inextricably coupled, and activation may represent a state of relative nutrient deprivation as demand exceeds supply. A major challenge is to model how metabolic pathways important for generating high-energy phosphates are modified to accommodate needs for biomass in the form of substrates, not just cofactors, for biosynthetic activity. In addition, advances in metabolomics are required to reveal how catabolic processes such as autophagy and protein degradation are critical to maintain substrate and metabolite levels that support the bioenergetic and biosynthetic needs of stem cells activating out of quiescence.

Editing Cellular Energetics

Juan Carlos Izpisua Belmonte
Salk Institute

Mitochondria play fundamental roles in energy production and metabolism, and mutations in mitochondrial DNA (mtDNA) lead to devastating maternally inherited disorders. Recent reports show that mutant mtDNA can be spontaneously reduced during iPSC reprogramming or specifically eliminated from somatic cells using gene editing tools. These advances will help guide the development of new cell therapies for mitochondrial diseases. Though these advances are encouraging, somatic cell approaches cannot always prevent mitochondrial disease transmission to the next generation. Prenatal diagnosis, while useful, fails to completely prevent transmission of mitochondrial diseases due to the random segregation of mtDNA. Thus, germline modifications are needed to correct such disorders. Mitochondrial replacement techniques, which require the use of healthy donor oocytes or embryos, are currently being developed and are under evaluation by government authorities. In parallel, the development of new mtDNA gene editing technologies may not be that far away. mtDNA gene editing techniques, when applied to the patient's own oocytes, may revolutionize the treatment and transmission of mitochondrial diseases to our descendants. Notwithstanding the hopes that these advances bring, it is our responsibility as scientists to inform and seek guidance from our society on discoveries made in the laboratory that may alter not only the course of certain human diseases but even the evolution of our own species.

The Ecology of DNA

Miguel Ramalho-Santos
University of California, San Francisco

In the news, epigenetics is portrayed as something having to do with your health being affected by what your mother ate or how stressed she was. Psychologists talk about an epigenetic succession of developmental stages of the human psyche. Let's call this the world of macro epigenetics. In the lab we talk about epigenetics as replicative chemistry on DNA, histones and noncoding RNA in stem cells and the germline. Let's call this the world of micro epigenetics. I would like to know how much the worlds of macro and micro epigenetics overlap, and how much metabolites acting in stem cells mediate such overlap. I suspect that some metabolites like acetyl-CoA are as much second messengers as cyclic AMP. Some nutrients like vitamin C are as much hormones as estrogen. All these voices talk to chromatin. In a future "theory of everything epigenetics" that connects our DNA all the way up to our ecosystems, I hope that we will factor in the two broad implications of such connections: (1) pollution and climate change are problems of profound epigenetic consequence, rather than solely the realm of ecologists; and (2) the ecosystems within us speak to us as much as those without. When Walt Whitman wrote, "I am large, I contain multitudes," he could have been referring to the way our microbiome modulates our environment, and the way our transposable elements modulate our responses. We are symbionts, and long have been, and epigenetics holds our improbable balance together well before birth all the way to dusty death.

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Metabolism-Directed Regeneration

Andre Terzic
Mayo Clinic

At the vanguard of future healthcare, regenerative biology aims to address the unmet needs of an aging global population vulnerable to chronic diseases. Decoding the mechanisms of tissue renewal versus degeneration, in the context of senescence and disease burden, has provided the foundation for regenerative paradigms. Translating the principles of natural rejuvenation will, in turn, pave the way for novel reparative strategies and the establishment of a science-driven regenerative medicine model of care.

The way stem cells use energy and intermediate metabolites determines their function and ultimate fate. Plasticity in stem cell metabolism is increasingly recognized to be critical in support of embryonic development, adult tissue homeostasis, and innate healing throughout life. Metabolism-dependent regulation of epigenetics plays a key role in directing cellular fate beyond matching energetic demands of stage-specific states, and enables stem cells and their progeny to communicate and respond to changes occurring within local niches in health and disease. The aging/disease phenotype has independently been associated with a decline in energy metabolism and stem cell function, yet how they interact in pathology remains unexamined. By exploring the interface of these fields, we hope to aid in the development of therapeutic techniques that offer individualized beneficial outcomes through targeting energy metabolism in stem cells for sustained rejuvenation of aging and diseased tissues.

Metabolism of Old Stem Cells

Anne Brunet
Stanford University

Aging is accompanied by a decline in tissue regeneration and adult stem cell function, which may underlie frailty and system failure in old age. Intriguingly, many genetic and environmental strategies that delay organismal aging point to metabolic pathways, such as the insulin-FOXO, mTOR, and AMPK pathways. Recent evidence indicates that these central longevity pathways play a key role in adult stem cell maintenance. It will be exciting to explore how aging and longevity pathways alter the metabolic state of stem cells and whether an old metabolism can be "rejuvenated" to a younger one to improve stem cell function. It is striking to note that metabolites are often used as cofactors for enzymes that modulate chromatin states, which are key for cell fate determination. Deciphering the connection between metabolism and epigenetic states in stem cells should provide key insights into how long-lasting changes to stem cell fate are implemented and how they change throughout life. Finally, the advent of new technologies is allowing the identification of novel metabolites in single cells or in blood. These advances have the potential to reveal new metabolic pathways within stem cells and to decipher new modes of communication between stem cells and other cell types within a tissue or at a distance via the blood circulation. Looking forward, specific metabolites could be developed as small molecules to preserve stem cell function and prevent general demise during aging.

Metabolism Dictates Cell Fate

Navdeep S. Chandel
Northwestern University

The resurgence of interest in metabolism in the cancer field has metastasized to the stem cell field. Currently, there are two key aspects that I find exciting in this area. First, we are working to delineate metabolic programs in stem, progenitor, and differentiated cells. We ask, "What are the metabolic pathways and necessary fuels that maintain and distinguish each of these cell populations?" An interesting consideration is whether rapidly proliferating stem cells utilize different metabolic programs from rapidly proliferating cancer cells. Resolving these questions will rely on advances in metabolomics combined with genetic manipulation of metabolic pathways. Identification of such differences could revolutionize cancer therapy by allowing more specific targeting of cancer and avoiding bystander damage to healthy stem and progenitor cells.

A second provocative question is whether metabolism can dictate stem cell renewal and/or differentiation. It is well known that signaling pathways converge on specific transcriptional networks to promote stem cell self-renewal and differentiation. Conventionally, it is thought that metabolism is altered as a consequence of the chosen cell fate—that is, metabolic demand drives the cell's metabolic program. However, emerging data suggest that metabolism itself can alter transcriptional networks to dictate cell fate, paving the way for the possibility that we might someday be able to regulate stem cells through modulation of metabolism.

Metabolomics of Leukemic Niches

Dominique Bonnet
London Research Institute

Over the past decade, our understanding of the extrinsic signals generated by the surrounding bone marrow microenvironment that controls whether hematopoietic stem cells (HSCs) self-renew, differentiate, or remain quiescent has increased significantly. At the same time, in the hematopoietic system, little is known about the metabolic status and dependencies of HSCs and progenitors. In my view, how HSC metabolism is modulated by inflammation and stress and the consequences of these alterations warrant further investigation. It is clear that the increased energetic demands required for the deregulated proliferation and survival of cancer cells often results in an altered metabolic profile within these cells via both cell-autonomous signals and cues from the microenvironment. The consequence of a tumor cell's altered metabolic profile may, in turn, also have an impact on its neighboring niche cells through the release of metabolic byproducts. Such metabolites could affect niche cell function by acting as ligands for transcription factors and/or substrates for metabolic pathways or by modifying innate immune cell fate. Therefore, investigations into this metabolic cross-talk between leukemia cells and their microenvironment via, possibly, the use of in vivo imaging techniques should provide an exciting further insight into our current understanding of leukemia initiation and development and may provide therapeutic benefit in the future.

Aging Stem Cell Metabolism

Heinrich Jasper
Buck Institute

Stem cell dysfunction is a hallmark of aging. The widespread decline in regenerative capacity associated with aging is increasingly recognized as a critical driver of tissue degeneration and associated age-related diseases. Metabolic deregulation, both systemically and locally, is tightly linked to these phenotypes. How stem cell metabolism is adversely affected in aging tissues, whether such changes are a consequence of systemic metabolic changes or stem-cell-intrinsic molecular changes, and whether interventions to "rejuvenate" stem cell metabolism are viable strategies to improve regeneration in aging tissues are all pressing questions that the field is starting to explore. I believe that a combination of advanced "-omics" approaches with genetic studies that aim for in vivo characterization and perturbation of regenerative function in model organisms is going to be the central strategy to resolve some of these questions in the future. Clearly, such strategies have already generated exciting new insight into the interaction of stem cells with their local and systemic environment, factors influencing stem cell metabolism in aging tissues, and possible rejuvenating interventions. It can be anticipated that we will continue to make significant advances in this area in the next few years, and these will contribute to our goal of identifying targeted interventions that allay and delay age-related pathologies.